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Hide?	Set Name	Query	Hit Count
		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR	
☐	L53	(vasopressin)adj(levels)same(hypercalcemia)	0
☐	L52	(low)adj(vasopresin)adj(levels)same(hypercalcemia)	0
☐	L51	(vasopressin)adj(levels)same(tumor)	6
		DB=USPT; PLUR=YES; OP=OR	
☐	L50	5798225.pn.	1
☐	L49	5695955.pn.	1
☐	L48	5693616.pn.	1
☐	L47	5584592.pn.	1
☐	L46	5395824.pn.	1
☐	L45	5149779.pn.	1
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☐	L44	9918945	2
		DB=EPAB; PLUR=YES; OP=OR	
☐	L43	WO-9851329-A1.did.	1
		DB=DWPI; PLUR=YES; OP=OR	
☐	L42	9851329	2
		DB=USPT; PLUR=YES; OP=OR	
☐	L41	L38 and (PTHrP)adj(antibod?)	2
☐	L40	L38 and PTHrP	18
☐	L39	L38 and anti-PTHrP	2
☐	L38	424/130.1 133.1, 134.1, 145.1, 178.1.ccls.	9988
		DB=EPAB; PLUR=YES; OP=OR	
☐	L37	WO-9633735-A1.did.	1
		DB=DWPI; PLUR=YES; OP=OR	
☐	L36	9633735	1
		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR	
☐	L35	(arginine)adj(vasopressin)adj(levels)	3
☐	L34	L33 and antibod?	7
☐	L33	L32 and treatment	93
☐	L32	(vasopressin)adj(level)	101
☐	L31	L30 and diabetes	54

☐	L30	L21 and hypercalcemia	56
☐	L29	(FERM)adj(BP-5631)	11
☐	L28	L25 and treatment	44
☐	L27	L26 and vasopressin	3
☐	L26	L25 and cancer	40
☐	L25	anti-PTHrP	51
☐	L24	L21 and (parathyroid)adj(hormone)adj(related)adj(protein)	2
☐	L23	L21 and anti-PTHrP	0
☐	L22	L21 and PTHrP	5
☐	L21	(vasopressin)same(cancer)	625
☐	L20	L19 and vasopressin	33
☐	L19	(azuma)adjadj(yumiko)	38186
☐	L18	(tsunenari)adj(toshiaki)	24
☐	L17	(onuma)adj(etsuro)	8
☐	L16	L15 and vassopressin	0
☐	L15	(ogata)adj(etsuro)	17
☐	L14	(vassopressin)same(PTHrP)same(antibod?)	0
☐	L13	(vassopressin)same(anti-PTHrP)	0
☐	L12	L11 and anti-PTHrP	2
☐	L11	(vasopressin)same(parathyroid)adj(hormone)adj(related)adj(peptide)	36
	DB=JPAB; PLUR=YES; OP=OR		
☐	L10	4-228089	0
☐	L9	jp 4228089	8200370
	DB=JPAB,DWPI; PLUR=YES; OP=OR		
☐	L8	jp 4228089	16542856
	DB=JPAB; PLUR=YES; OP=OR		
☐	L7	4228089	0
	DB=EPAB; PLUR=YES; OP=OR		
☐	L6	WO-9217602-A1.did.	1
	DB=DWPI; PLUR=YES; OP=OR		
☐	L5	9217602	2
	DB=EPAB; PLUR=YES; OP=OR		
☐	L4	EP-962467-A1.did.	1
	DB=DWPI; PLUR=YES; OP=OR		
☐	L3	9813388	2
	DB=USPT; PLUR=YES; OP=OR		
☐	L2	5001223.pn.	1
☐	L1	6903194.pn.	1

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NEWS 3	AUG 06	FSTA enhanced with new thesaurus edition
NEWS 4	AUG 13	CA/CAplus enhanced with additional kind codes for granted patents
NEWS 5	AUG 20	CA/CAplus enhanced with CAS indexing in pre-1907 records
NEWS 6	AUG 27	Full-text patent databases enhanced with predefined patent family display formats from INPADOCDB
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NEWS 9	SEP 07	STN AnaVist, Version 2.0, now available with Derwent World Patents Index
NEWS 10	SEP 13	FORIS renamed to SOFIS
NEWS 11	SEP 13	INPADOCDB enhanced with monthly SDI frequency
NEWS 12	SEP 17	CA/CAplus enhanced with printed CA page images from 1967-1998
NEWS 13	SEP 17	CAplus coverage extended to include traditional medicine patents
NEWS 14	SEP 24	EMBASE, EMBAL, and LEMBASE reloaded with enhancements
NEWS 15	OCT 02	CA/CAplus enhanced with pre-1907 records from Chemisches Zentralblatt
NEWS 16	OCT 19	BEILSTEIN updated with new compounds
NEWS 17	NOV 15	Derwent Indian patent publication number format enhanced
NEWS 18	NOV 19	WPIX enhanced with XML display format
NEWS 19	NOV 30	ICSD reloaded with enhancements
NEWS 20	DEC 04	LINPADOCDB now available on STN

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 NEWS 21  DEC 14  BEILSTEIN pricing structure to change
 NEWS 22  DEC 17  USPATOLD added to additional database clusters
 NEWS 23  DEC 17  IMSDRUGCONF removed from database clusters and STN
 NEWS 24  DEC 17  DGENE now includes more than 10 million sequences
 NEWS 25  DEC 17  TOXCENTER enhanced with 2008 MeSH vocabulary in
                  MEDLINE segment
 NEWS 26  DEC 17  MEDLINE and LMEDLINE updated with 2008 MeSH vocabulary
 NEWS 27  DEC 17  CA/CAplus enhanced with new custom IPC display formats
 NEWS 28  DEC 17  STN Viewer enhanced with full-text patent content
                  from USPATOLD
 NEWS 29  JAN 02  STN pricing information for 2008 now available
 NEWS 30  JAN 16  CAS patent coverage enhanced to include exemplified
                  prophetic substances

 NEWS EXPRESS  19 SEPTEMBER 2007:  CURRENT WINDOWS VERSION IS V8.2,
               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 19 SEPTEMBER 2007.

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=> s humanized antibod?
L1         3157 HUMANIZED ANTIBOD?

=> s l1 and PTHrP
L2           16 L1 AND PTHRP

=> dup remove l2
PROCESSING COMPLETED FOR L2
L3           10 DUP REMOVE L2 (6 DUPLICATES REMOVED)
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=> s l3 and pd<20000720
   2 FILES SEARCHED...
L4            2 L3 AND PD<20000720

=> d l4 cbib abs

L4   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2008 ACS on STN
2001:30858   Document No. 135:59794  The application of BIA technology in the
     optimization of humanized mouse anti-parathyroid hormone-related protein (
     PTHrP) antibodies.  Esaki, Keiko (Pharmaceutical Technology Lab.,
     Chugai Pharmaceutical Co., Ltd., Gotemba, 412-8513, Japan).  Real-Time
     Analysis of Biomolecular Interactions, 195-200.  Editor(s): Nagata,
     Kazuhiro; Handa, Hiroshi.  Springer-Verlag Tokyo: Tokyo, Japan. (English)
     2000.  CODEN: 69AUQB.
AB   A review with 5 refs.  Topics discussed include the preparation of the sensor
     chip surface; the interaction between mouse monoclonal antibodies and the
     immobilized [Cys35]-PTHrP(1-35); optimization of
     humanized antibodies; and the kinetic anal. of
     humanized antibodies and the immobilized [Cys35]-
     PTHrP(1-35).


=> d l4 1-2 cbib abs

L4   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2008 ACS on STN
2001:30858   Document No. 135:59794  The application of BIA technology in the
     optimization of humanized mouse anti-parathyroid hormone-related protein (
     PTHrP) antibodies.  Esaki, Keiko (Pharmaceutical Technology Lab.,
     Chugai Pharmaceutical Co., Ltd., Gotemba, 412-8513, Japan).  Real-Time
     Analysis of Biomolecular Interactions, 195-200.  Editor(s): Nagata,
     Kazuhiro; Handa, Hiroshi.  Springer-Verlag Tokyo: Tokyo, Japan. (English)
     2000.  CODEN: 69AUQB.
AB   A review with 5 refs.  Topics discussed include the preparation of the sensor
     chip surface; the interaction between mouse monoclonal antibodies and the
     immobilized [Cys35]-PTHrP(1-35); optimization of
     humanized antibodies; and the kinetic anal. of
     humanized antibodies and the immobilized [Cys35]-
     PTHrP(1-35).

L4   ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2008 ACS on STN
1998:210769   Document No. 128:293971  Antibody against human parathormone
     related peptides.  Sato, Kou; Wakahara, Yuji; Yabuta, Naohiro (Chugai
     Seiyaku K. K., Japan; Sato, Kou; Wakahara, Yuji; Yabuta, Naohiro).  PCT
     Int. Appl. WO 9813388 A1 19980402, 184 pp.  DESIGNATED STATES:
     W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK,
     EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, KE, KG, KR, KZ, LC, LK, LR, LS,
     LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG,
     SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG,
     KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES,
     FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG.
     (Japanese).  CODEN: PIXXD2.  APPLICATION: WO 1997-JP3382 19970924.
     PRIORITY: JP 1996-255196 19960926; JP 1997-214168 19970724.
AB   An antibody against human parathormone related peptides (hPTHrP), a DNA
     encoding the antibody, a recombinant vector containing the DNA, a transformant
     prepared with the vector, a process for producing the antibody, and the
     application of the antibody.  These humanized anti-hPTHrP antibody
     fragments are useful for treating hypercalcemia accompanying malignancy or
     hypophosphatemia.


=> s anti-hPTHrP
L5            16 ANTI-HPTHRP

=> s l5 and treat?
```

```
L6            1 L5 AND TREAT?

=> d l6 cbib abs

L6   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2008 ACS on STN
1998:210769   Document No. 128:293971  Antibody against human parathormone
     related peptides.  Sato, Kou; Wakahara, Yuji; Yabuta, Naohiro (Chugai
     Seiyaku K. K., Japan; Sato, Kou; Wakahara, Yuji; Yabuta, Naohiro).  PCT
     Int. Appl. WO 9813388 A1 19980402, 184 pp.  DESIGNATED STATES: W:  AL, AM,
     AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI,
     GB, GE, GH, HU, ID, IL, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV,
     MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,
     TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU,
     TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA,
     GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG.  (Japanese).
     CODEN: PIXXD2.  APPLICATION: WO 1997-JP3382 19970924.  PRIORITY: JP
     1996-255196 19960926; JP 1997-214168 19970724.
AB   An antibody against human parathormone related peptides (hPTHrP), a DNA
     encoding the antibody, a recombinant vector containing the DNA, a transformant
     prepared with the vector, a process for producing the antibody, and the
     application of the antibody.  These humanized anti-
     hPTHrP antibody fragments are useful for treating
     hypercalcemia accompanying malignancy or hypophosphatemia.


=> s treat?
L7    13159831 TREAT?

=> s l7 and hypercalcemia
L8        16983 L7 AND HYPERCALCEMIA

=> s l8 and polyuria
L9          212 L8 AND POLYURIA

=> s l9 and antibod?
L10          10 L9 AND ANTIBOD?

=> s l10 and PTHrP1-34
L11           0 L10 AND PTHRP1-34

=> s l10 and PTHrP
L12           4 L10 AND PTHRP

=> dup remove l12
PROCESSING COMPLETED FOR L12
L13           2 DUP REMOVE L12 (2 DUPLICATES REMOVED)

=> d l13 1-2 cbib abs

L13  ANSWER 1 OF 2     MEDLINE on STN
2006057279.    PubMed ID: 16444366.    [Hypercalcemia of malignancy:
     clinical features, diagnosis and treatment].    A hipercalcemia
     nas malignidades: aspectos clinicos, diagnosticos e terapeuticos. Farias
     Maria Lucia F de. (Faculdade de Medicina, Universidade Federal do Rio de
     Janeiro, RJ.. fleiuss@hucff.ufrj.br) . Arquivos brasileiros de
     endocrinologia e metabologia, (2005 Oct) Vol. 49, No. 5, pp. 816-24.
     Electronic Publication: 2006-01-23. Ref: 64. Journal code: 0403437. ISSN:
     0004-2730. Pub. country: Brazil. Language: Portuguese.
AB   Hypercalcemia associated with malignancies is reported in up to
     20 to 30% of patients with cancer during the course of the disease, and
     points to a poor prognosis.  Symptoms related to the central nervous
     system, as progressive mental impairment, stupor and coma, predominate.
     Alterations in kidney function (water-concentrating defect leading to
     polyuria) and gastrointestinal tract (anorexia, nausea, vomiting)
     corroborate to dehydration and a further increase in serum calcium.
```

Cancer-induced **hypercalcemia** may be classified as: 1) local osteolytic **hypercalcemia** (LOH), due to marked increase in osteoclastic bone resorption in areas surrounding the malignant cells within the marrow space; 2) humoral **hypercalcemia** of malignancy, caused by the secretion of parathyroid hormone-related protein (**PTHrP**) by the malignant tumor; 3) ectopic hyperparathyroidism; 4) 1,25(OH)2 D-secreting tumors. Adequate control of **hypercalcemia** is necessary to give the patient time to respond to anti-cancer therapy. Volume expansion with saline will correct dehydration, improve glomerular filtration and increase urinary calcium excretion, which may be further stimulated by loop diuretics. Intravenous bisphosphonates are the most effective agents to control **hypercalcemia**, as they block osteoclastic osteolysis and also have antitumoral effects, decreasing bone metastases. New approaches to control the skeletal manifestations of malignancies are anti-**PTHrP** and anti-RANKL **antibodies**, osteoprotegerin, and also proteasome inhibitors in the case of multiple myeloma.

L13 ANSWER 2 OF 2 MEDLINE on STN DUPLICATE 1
2003534792. PubMed ID: 14613038. **Treatment** of malignancy-associated **hypercalcemia** and cachexia with humanized anti-parathyroid hormone-related protein **antibody.** Sato Koh; Onuma Etsuro; Yocum Richard C; Ogata Etsuro. (Department of International Coordination, Chugai Pharmaceutical Co, Ltd, Skizuuoka, Japan.) Seminars in oncology, (2003 Oct) Vol. 30, No. 5 Suppl 16, pp. 167-73. Ref: 11. Journal code: 0420432. ISSN: 0093-7754. Pub. country: United States. Language: English.

AB Parathyroid hormone-related protein (**PTHrP**) plays a central role in humoral **hypercalcemia** of malignancy (HHM), which is one of the most frequent paraneoplastic syndromes. **PTHrP** produced by the tumor acts through a common PTH/**PTHrP** receptor to promote bone resorption, inhibit calcium excretion from the kidney, and induce **hypercalcemia.** Patients with HHM often develop cachexia associated with typical symptoms such as anorexia, malaise, nausea, constipation, **polyuria**, polydipsia, and confusion. The etiology of the cachexia is not fully understood but is thought to be caused by **hypercalcemia** and various cytokines such as interleukin-6, tumor necrosis factor-alpha, leukemia inhibitory factor, and others. In this study, we investigated the role of **PTHrP** in **hypercalcemia** and cachexia in HHM by using humanized anti-**PTHrP antibody.** A mouse monoclonal **antibody** that binds to **PTHrP** amino acid sequence 1-34 and inhibits **PTHrP** function has been humanized to create a specific and potent agent for the **treatment** of patients with HHM. The mouse monoclonal **antibody** has been shown to have antihypercalcemic activity against nude mice bearing human tumors. Because a mouse **antibody** is highly immunogenic in human patients, the complementarity-determining regions from the mouse **antibody** were grafted into a human **antibody.** The resulting humanized **antibody** specifically recognizes **PTHrP**(1-34) and neutralizes **PTHrP** functions in vitro and in vivo. The humanized anti-**PTHrP antibody** was administered intravenously to HHM model animals bearing tumors such as LC-6 human lung carcinoma. These animals showed symptoms similar to those of patients with HHM (eg, **hypercalcemia** and cachexia). The humanized anti-**PTHrP antibody-treated** animals responded with normalization of blood ionized calcium level through an improvement of bone metabolism and calcium excretion. Moreover, the **treated** animals also showed an improvement in body weight, ultromotivity, metabolic alkalosis, food consumption, water intake, serum phosphorus, and renal function. Consequently, the humanized **antibody-treated** animals experienced complete resolution of **hypercalcemia** and cachexia. These results suggest that the humanized **antibody** would be an effective and beneficial agent for patients with HHM, and that **PTHrP** is a major pathogenetic factor of **hypercalcemia**

and cachexia in patients with HHM.

=> s vasopressin level
L14 3234 VASOPRESSIN LEVEL

=> s l14 and brain
L15 518 L14 AND BRAIN

=> s l15 and maintain
L16 13 L15 AND MAINTAIN

=> dup remove l16
PROCESSING COMPLETED FOR L16
L17 8 DUP REMOVE L16 (5 DUPLICATES REMOVED)

=> d l17 1-8 cbib abs

L17 ANSWER 1 OF 8 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN
2004138192 EMBASE New additions to the intensive care armamentarium. Rice T.W.; Bernard G.R.. Dr. T.W. Rice, Div. Allergy, Pulmon./Crit. Care M., Vanderbilt Univ. School of Medicine, Center for Lung Research, Nashville, TN 37232-2650, United States. todd.rice@vanderbilt.edu. Drugs of Today Vol. 40, No. 2, pp. 157-170 Feb 2004.
Refs: 107.
ISSN: 0025-7656. CODEN: MDACAP
Pub. Country: Spain. Language: English. Summary Language: English.
Entered STN: 20040415. Last Updated on STN: 20040415
AB Many advances have improved the care of critically ill patients, but only a few have been through the use of pharmaceutical agents. Recently, the US Food and Drug Administration (FDA) approved drotrecogin alfa (activated), or recombinant human activated protein C, for the treatment of patients with a high risk of death from severe sepsis. Drotrecogin alfa (activated) has antiinflammatory, antithrombotic and fibrinolytic properties. When given as a continuous intravenous infusion, recombinant human activated protein C decreases absolute mortality of severely septic patients by 6.1%, resulting in a 19.4% relative reduction in mortality. The absolute reduction in mortality increases to 13% if the population treated is restricted to patients with an APACHE II score greater than 24, as suggested by the FDA. The most frequent and serious side effect is bleeding. Severe bleeds increased from 2% in patients given placebo to 3.5% in patients receiving drotrecogin alfa (activated). The risk of bleeding was only increased during the actual infusion time of the drug, and the bleeding risk returned to placebo levels 24 hours after the infusion was discontinued. Patients treated in the intensive care unit frequently develop anemia, usually severe enough to require at least one transfusion of red blood cells. With the recent discovery of the harmful effects of allogeneic red blood cell transfusions and the increasing shortage of available red blood cell products, emphasis has been placed on minimizing transfusions. Patients who receive exogenous recombinant human erythropoietin **maintain** higher hemoglobin levels, in spite of requiring fewer transfusions during their stay in the intensive care unit. Recombinant human erythropoietin appears to be effective whether it is given as 300 units/kg of body weight subcutaneously every other day or as 40,000 units subcutaneously every week. Differences in hemoglobin values were not apparent until at least one week of therapy, but they continued to diverge after that initial week. Furthermore, the incidence of adverse events was similar to that of patients receiving placebo and there was no difference in mortality, suggesting that avoidance of blood transfusions did not translate into increased survival. Thus, recombinant human erythropoietin appears to be both safe and effective in treating the anemia found in critically ill patients, but it is less clear that such treatment is cost effective, especially in the higher dose regimens. Hypotension in patients with septic shock is often difficult to correct.

Despite enormous dosages of catecholamines, many of these patients continue to have inadequate blood pressures. Inadequate levels of vasopressin have been identified in patients with septic shock, as well as in other patients with hypotension secondary to refractory vasodilatation. Vasopressin is a peptide hormone secreted from the posterior pituitary in response to hyperosmolality, hypovolemia or hypotension. Levels of vasopressin initially rise in patients with septic shock, but as hypotension persists, **vasopressin levels** fall below normal. Administration of exogenous vasopressin in physiologic dosages significantly increases blood pressure in patients with shock associated with sepsis and other vasodilatory states. This rise in blood pressure is often significant enough that endogenous catecholamines can be decreased and frequently discontinued entirely. Early withdrawal of the vasopressin replacement infusion results in recurrent hypotension. Unfortunately, randomized, blinded, placebo-controlled trials showing improvement in long-term outcomes such as mortality and length of stay are still lacking.

L17 ANSWER 2 OF 8 MEDLINE on STN DUPLICATE 1

1998278559. PubMed ID: 9617997. Nitric oxide control of drinking, vasopressin and oxytocin release and blood pressure in dehydrated rats. Liu H; Terrell M L; Bui V; Summy-Long J Y; Kadekaro M. (Division of Neurosurgery, the University of Texas Medical Branch at Galveston, 77555-0517, USA.) Physiology & behavior, (1998 Mar) Vol. 63, No. 5, pp. 763-9. Journal code: 0151504. ISSN: 0031-9384. Pub. country: United States. Language: English.

AB Intracerebroventricular (i.c.v.) injection of the inhibitor of NO synthase (NOS), N(G)-nitro-L-arginine methyl ester (L-NAME) (250 microg/5 microL) attenuated the drinking response in rats deprived of water for 24 h. Moreover, oxytocin (OT) levels in plasma increased after 2 min, whereas both oxytocin and **vasopressin levels** were elevated at 120 min after intracerebroventricular injection. The delayed effect of L-NAME on both hormones was not observed in dehydrated animals allowed to drink water. Blood pressure remained stable after injection of artificial cerebrospinal fluid (aCSF) in dehydrated rats not allowed to drink. In rats having access to water, however, there was an immediate but transient pressor response (0-5 min) with a delayed hypotension from 45 to 120 min. L-NAME consistently increased blood pressure in a biphasic mode, whether the animals drank or not, with an early peak at 5 min that decayed after 15-30 min and a second pressor response beginning at 30-45 min and remaining elevated at 120 min when the experiment ended. These pressor responses were independent of the adrenal glands. Thus, centrally produced nitric oxide facilitates drinking, inhibits release of vasopressin and oxytocin from the magnocellular system, and **maintains** resting arterial blood pressure in normally hydrated and dehydrated rats.

L17 ANSWER 3 OF 8 CAPLUS on STN

1994:103885 Document No. 120:103885 Effect of hypoxemia on the cardiovascular response to intracranial hypertension in postnatal lambs. Kearney, Marguerite L.; Backofen, Joanne E.; Koehler, Raymond C.; Jones, M. Douglas, Jr.; Traystman, Richard J. (Dep. Anesthesiol., Johns Hopkins Med. Inst., Baltimore, MD, 21287, USA). American Journal of Physiology, 265(5, Pt. 2), H1557--H1563 (English) 1993. CODEN: AJPHAP. ISSN: 0002-9513.

AB Large increases in intracranial pressure in fetal sheep result in more potent peripheral vasoconstriction and better maintenance of cerebral O2 consumption (CMRO2) than in postnatal sheep. The fetus is exposed to a lower PO2. The authors tested the hypothesis that low PO2 in postnatal lambs potentiates peripheral vasoconstriction and better **maintains** cerebral perfusion pressure and CMRO2. Pentobarbital-anesthetized lambs, 2-7 days old, were ventilated with either room air (n -7) or a low O2 mixture to reduce arterial O2 saturation to 50% (n = 7). Elevation of intracranial pressure to within 3-5 mmHg of baseline mean arterial pressure for 30 min by ventricular fluid infusion initially caused a

similar increase in arterial pressure in the normoxic [11 ± 3 (SE) mmHg] and hypoxic (14 ± 2 mmHg) groups. Plasma catecholamines increased more rapidly in the hypoxic group. However, plasma **vasopressin levels** were substantially elevated by hypoxia alone and failed to increase further with elevated intracranial pressure. Moreover, there was no significant difference between groups in the steady-state increase in arterial pressure, and microsphere-determined blood flow to intestines, kidney, skin, and muscle did not decrease in either group. Consequently, cerebral perfusion pressure, regional cerebral blood flow, and CMRO2 were reduced similarly in both groups. Therefore, hypoxemia failed to potentiate the postnatal pressor response. Low PO2 is unlikely to be the major mechanism for the potent Cushing response in the fetus.

L17 ANSWER 4 OF 8 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

1993348201 EMBASE Effect of hypoxemia on the cardiovascular response to intracranial hypertension in postnatal lambs. Kearney M.L.; Backofen J.E.; Koehler R.C.; Jones Jr. M.D.; Traystman R.J.. R.C. Koehler, Anesthesiology/Crit. Care Med. Dept., Blalock 1404, Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21287-4961, United States. American Journal of Physiology - Heart and Circulatory Physiology Vol. 265, No. 5 34-5, pp. H1557-H1563 1993.
ISSN: 0002-9513. CODEN: AJPPDI
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 931226. Last Updated on STN: 931226

AB Large increases in intracranial pressure in fetal sheep result in more potent peripheral vasoconstriction and better maintenance of cerebral O(2) consumption (CMR(O(2))) than in postnatal sheep. The fetus is exposed to a lower PO(2). We tested the hypothesis that low PO(2) in postnatal lambs potentiates peripheral vasoconstriction and better **maintains** cerebral perfusion pressure and CMR(O(2)). Pentobarbital-anesthetized lambs, 2-7 days old, were ventilated with either room air (n = 7) or a low O(2) mixture to reduce arterial O(2) saturation to 50% (n = 7). Elevation of intracranial pressure to within 3-5 mmHg of baseline mean arterial pressure for 30 min by ventricular fluid infusion initially caused a similar increase in arterial pressure in the normoxic [11 ± 3 (SE) mmHg] and hypoxic (14 ± 2 mmHg) groups. Plasma catecholamines increased more rapidly in the hypoxic group. However, plasma **vasopressin levels** were substantially elevated by hypoxia alone and failed to increase further with elevated intracranial pressure. Moreover, there was no significant difference between groups in the steady- state increase in arterial pressure, and microsphere-determined blood flow to intestines, kidney, skin, and muscle did not decrease in either group. Consequently, cerebral perfusion pressure, regional cerebral blood flow, and CMR(O(2)) were reduced similarly in both groups. Therefore, hypoxemia failed to potentiate the postnatal pressor response. Low PO(2) is unlikely to be the major mechanism for the potent Cushing response in the fetus.

L17 ANSWER 5 OF 8 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

1993099552 EMBASE Transient hyponatremia after damage to the neurohypophyseal tracts. Ultmann M.C.; Hoffmann G.E.; Nelson P.B.; Robinson A.G.. Dr. A.G. Robinson, E-1140 Biomedical Science Tower, University of Pittsburgh, Pittsburgh, PA 15261, United States. Neuroendocrinology Vol. 56, No. 6, pp. 803-811 1992.
ISSN: 0028-3835. CODEN: NUNDAJ
Pub. Country: Switzerland. Language: English. Summary Language: English.
Entered STN: 930516. Last Updated on STN: 930516

AB Section of the neurohypophyseal stalk classically produces a triphasic response: diabetes insipidus (1st phase), hyponatremia or normonatremia (2nd phase), and diabetes insipidus (3rd phase). Transient hyponatremia without diabetes insipidus has been reported after transsphenoidal pituitary surgery. We report two additional cases of transient

hyponatremia which occurred 6-8 days after pituitary surgery. We hypothesize that this outcome may be due to partial section or damage of the hypothalamiconeurohypophyseal tracts. The remaining intact vasopressin neurons function normally to protect against the diabetes insipidus of the first and third phase, but leak of vasopressin from the damaged tracts and posterior pituitary is sufficient to cause what can be described as an isolated second phase. To study this hypothesis in rats, partial damage to the hypothalamicneurohypophyseal tracts was produced by radio-frequency lesions. The lesions did not affect anterior pituitary function. A variety of responses in posterior pituitary function occurred, including classic triphasic response in 2 rats and transient hyponatremia in 20 of 35 lesioned animals. The mean sodium nadir was 128.7 ± 1.5 mEq/l in comparison to the sham-operated value of 140.0 ± 0.4 mEq/l. Of the 20 rats exhibiting transient hyponatremia, 12 went on to develop diabetes insipidus, and 8 recovered. In the recovered group, the transient hyponatremia occurred 1-3 days after lesioning and returned to normal by day 7 which corresponds to the timing of the second phase of the triphasic response in rats. Hyponatremia was accompanied by **vasopressin levels** inappropriate for the plasma sodium level, inappropriately concentrated urine, water retention, and natriuresis. Animals that recovered from hyponatremia had sufficient vasopressin function to **maintain** normal plasma sodium with normal levels of fluid intake and were able to tolerate 30 h of fluid deprivation with minimal dehydration and elevation of plasma sodium. However, in this group, the vasopressin release in response to hypertonic saline infusion was attenuated. At sacrifice immunohistochemistry of neurophysin was performed, and a portion of the hypothalamiconeurohypophyseal tract in the internal zone of the median eminence was found to be intact in all animals which recovered, i.e., there was partial section. Thus, in both the patients and in the animals, the transient hyponatremia had the characteristic etiology, timing, and duration of an isolated second phase of the triphasic response.

L17 ANSWER 6 OF 8 MEDLINE on STN DUPLICATE 2

91064033. PubMed ID: 2147376. The role of arginine vasopressin in alcohol tolerance. Hoffman P L; Ishizawa H; Giri P R; Dave J R; Grant K A; Liu L I; Gulya K; Tabakoff B. (Division of Intramural Clinical and Biological Research, National Institute on Alcohol Abuse and Alcoholism, Bethesda, Maryland.) Annals of medicine, (1990) Vol. 22, No. 4, pp. 269-74. Ref: 47. Journal code: 8906388. ISSN: 0785-3890. Pub. country: Finland. Language: English.

AB Administration of the neuropeptide, arginine vasopressin, to animals that have acquired functional tolerance to ethanol will **maintain** such tolerance, even in the absence of further ethanol ingestion by the animals. In mice, this action of the peptide is mediated by central nervous system V1 receptors and requires intact **brain** noradrenergic systems. Autoradiographic studies have shown that some V1 receptors are localized presynaptically on catecholaminergic neuronal terminals in the mouse lateral septum, suggesting that vasopressin may act via modulation of catecholamine release. In addition, vasopressin has been found to increase mRNA levels for the proto-oncogene, c-fos, in septum and hippocampus, possibly by an action at postsynaptic receptors. Expression of c-fos, which has been hypothesized to play a role in central nervous system neuroadaptation, could transform short-term actions of vasopressin into long-term effects on ethanol tolerance. Studies with vasopressin antagonists indicate that the endogenous peptide influences tolerance, and therefore the effect of chronic ethanol ingestion on vasopressin synthesis and release was studied. In mice and rats, hypothalamic vasopressin mRNA is decreased by chronic ethanol exposure, although effects on plasma **vasopressin levels** differ in the two species. The effect of ethanol on extrahypothalamic vasopressin synthesis in **brain** is under investigation. The results suggest mechanisms by which vasopressin can produce long-term changes in central nervous system function, and provide evidence for a disturbance of vasopressin regulation during chronic ethanol ingestion.

L17 ANSWER 7 OF 8 MEDLINE on STN DUPLICATE 3

90072400. PubMed ID: 2589491. Absent effect of plasma vasopressin on rat **brain** blood flow during hemorrhage. Nakai M; Yamane Y; Umeda Y; Inada M; Yamamoto J; Kawamura M. (Department of Cardiovascular Dynamics, National Cardiovascular Center Research Institute, Osaka, Japan.) The American journal of physiology, (1989 Nov) Vol. 257, No. 5 Pt 2, pp. H1360-8. Journal code: 0370511. ISSN: 0002-9513. Pub. country: United States. Language: English.

AB We investigated whether a reflex increase in plasma **vasopressin level** due to hemorrhagic hypotension affects **brain** blood flow. In 60 lightly anesthetized, artificially ventilated rats, the flow was determined with radiolabeled microspheres. We found excellent maintenance of blood flow throughout all **brain** regions during the hypotensive state (71 mmHg on average), and such maintenance of flow was not modulated at all by a supramaximal intravenous dose of the selective vasopressin V1-receptor antagonist [d(CH2)5 Tyr-(Me)]AVP. The latter finding also implies that the V1 antagonist failed to unmask the vasodilator type actions of V2 receptors on the maintenance of flow during hemorrhagic hypotension. These were true also when the cervical sympathetic bundles were severed bilaterally. The plasma level of endogenous vasopressin was increased during hypotension, ranging from 118 to 973 pg/ml. Despite this increase, the **brain** blood flow was entirely independent of the plasma **vasopressin level** in all the **brain** regions studied. We conclude that the **brain** circulation of rats can **maintain** its blood flow during hemorrhagic hypotension without any apparent contribution from a concomitant reflex increase in plasma vasopressin. Despite our negative results for the **brain** blood flow, the possible segmental effects of circulating vasopressin on the **brain** arterial caliber remain to be clarified under conditions of hemorrhagic hypotension.

L17 ANSWER 8 OF 8 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

1990009855 EMBASE Absent effect of plasma vasopressin on rat **brain** blood flow during hemorrhage. Nakai M.; Yamane Y.; Umeda Y.; Inada M.; Yamamoto J.; Kawamura M.. M. Nakai, Dept. of Cardiovascular Dyn., Natl. Cardiov. Ctr. Res. Inst, Osaka 565, Japan. American Journal of Physiology - Heart and Circulatory Physiology Vol. 257, No. 5, pp. 26/5 1989. ISSN: 0002-9513. CODEN: AJPPDI
Pub. Country: United States. Language: English. Summary Language: English. Entered STN: 911213. Last Updated on STN: 911213

AB We investigated whether a reflex increase in plasma **vasopressin level** due to hemorrhagic hypotension affects **brain** blood flow. In 60 lightly anesthetized, artificially ventilated rats, the flow was determined with radiolabeled microspheres. We found excellent maintenance of blood flow throughout all **brain** regions during the hypotensive state (71 mmHg on average), and such maintenance of flow was not modulated at all by a supramaximal intravenous dose of the selective vasopressin V(1)-receptor antagonist [d(CH(2))(5)Tyr-(Me)]AVP. The latter finding also implies that the V(1) antagonist failed to unmask the vasodilator type actions of V(2) receptors on the maintenance of flow during hemorrhagic hypotension. These were true also when the cervical sympathetic bundles were severed bilaterally. The plasma level of endogenous vasopressin was increased during hypotension, ranging from 118 to 973 pg/ml. Despite this increase, the **brain** blood flow was entirely independent of the plasma **vasopressin level** in all the **brain** regions studied. We conclude that the **brain** circulation of rats can **maintain** its blood flow during hemorrhagic hypotension without any apparent contribution from a concomitant reflex increase in plasma vasopressin. Despite our negative results for the **brain** blood flow, the possible segmental effects of circulating vasopressin on the **brain** arterial caliber remain to be clarified under conditions of hemorrhagic hypotension.

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=> s blood vasopressin level
L18          28 BLOOD VASOPRESSIN LEVEL

=> s l18 and unpredictable
L19           0 L18 AND UNPREDICTABLE

=> s l18 and PTHrP
L20           0 L18 AND PTHRP

=> s l18 nd anti-PTHrP
MISSING OPERATOR L18 ND
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l18 and cancer
L21           0 L18 AND CANCER

=> dup remove l18
PROCESSING COMPLETED FOR L18
L22           18 DUP REMOVE L18 (10 DUPLICATES REMOVED)

=> s l22 and hypercalcemia
L23           0 L22 AND HYPERCALCEMIA

=> s l22 and pd<20000720
   2 FILES SEARCHED...
L24          17 L22 AND PD<20000720

=> d l24 1-17 cbib abs

L24  ANSWER 1 OF 17     MEDLINE on STN
1998232569.    PubMed ID: 9564057.   Endometrial Na+, K+-ATPase pump function
     and vasopressin levels during hysteroscopic surgery in patients pretreated
     with GnRH agonist. Taskin O; Buhur A; Birincioglu M; Burak F; Atmaca R;
     Yilmaz I; Wheeler J M. (Department of Obstetrics and Gynecology, Inonu
     University Medical School, Malatya, Turkey. ) The Journal of the American
     Association of Gynecologic Laparoscopists, (1998 May) Vol. 5,
     No. 2, pp. 119-24. Journal code: 9417443. ISSN: 1074-3804. Pub. country:
     United States. Language: English.
AB   STUDY OBJECTIVE: To investigate the effects of gonadotropin-releasing
     hormone (GnRH) analog pretreatment on endometrial Na+, K+-adenosine
     triphosphatase (ATPase) pump function and peripheral blood
     vasopressin levels, and their role in fluid absorption
     and mechanisms of hyponatremia in patients undergoing hysteroscopic
     endometrial ablation. DESIGN: Prospective, randomized, placebo-controlled
     study (Canadian Task Force classification I). SETTING:
     University-affiliated hospital. PATIENTS: Seventeen women with
     dysfunctional uterine bleeding. INTERVENTION: Nine women received a GnRH
     analog and eight received saline approximately 6 to 8 weeks before
     hysteroscopic ablation by electrosurgery. MEASUREMENTS and MAIN RESULTS:
     Both before randomization and immediately before surgery, endometrial
     biopsy samples were obtained and numbered consecutively without patient
     identification. Operative hysteroscopy was performed with glycine 1.5%
     mixed with 2% alcohol. The amount of irrigant and irrigant deficit; blood
     levels of albumin and ethanol; hematocrit and hemoglobin; changes in
     sodium levels; and central venous pressure were compared. The Na+,
     K+-ATPase pump activity was significantly increased in the GnRH analog
     group compared with the saline group and correlated with decreased
     estradiol levels (0.4 +/- 0.08 vs 0.26 +/- 0.06 micro mol/min/ml).
     Vasopressin levels were significantly lower in the GnRH group (3.2 +/- 0.9
     vs 7.6 +/- 1.7 micro mol/L). Mean volume of irrigant used and operating
     time were similar in both groups. Volume deficit, decrease in protein,
     and hematocrit were less in GnRH than in the saline group. Blood ethanol
     levels, decrease in sodium, and irrigant deficit were significantly lower
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in GnRH group. CONCLUSION: Pretreatment with GnRH analogs may prevent the adverse effects of estradiol on endometrial Na+, K+-ATPase and creates a protective mechanism against iatrogenic hyponatremia, which is more critical in women than men in case of absorption of irrigating fluid. Moreover, created hypoestrogenism may enhance Na+, K+-ATPase activity in brain as well as endometrium, thus decreasing women's susceptibility to hyponatremic complications and brain damage. Suppressed vasopressin levels may be protective against fluid absorption in GnRH analog-treated patients.

L24 ANSWER 2 OF 17 MEDLINE on STN

96144056. PubMed ID: 8587172. Acute myelogenous leukemia with diabetes insipidus without desmopression administration by anti-leukemic chemotherapy. Ino Y; Tsurumi H; Yamada T; Murakami N; Moriwaki H; Muto Y. (First Department of Internal Medicine, Gifu University School of Medicine.) [Rinsho ketsueki] The Japanese journal of clinical hematology, **(1995 Dec)** Vol. 36, No. 12, pp. 1359-64. Journal code: 2984782R. ISSN: 0485-1439. Pub. country: Japan. Language: Japanese.

AB We report a case of AML with diabetes insipidus (DI). A 68-year-old female was admitted to our hospital because of fever and leukocytosis. The WBC was 197,000/microliter with 98% blasts positive for myeloperoxidase, CD33, CD34 and HLA-DR. While, on admission, urine volume was more than 6 liters daily. **Blood vasopressin level** was 0.3 microgram/ml. The patient was diagnosed as having AML with DI. By chemotherapy consisting of BHAC, DNR, 6-MP and PSL and intrathecal administration of AraC, MTX and PSL, and nasal drip of DDAVP, complete remission was attained and the urine volume was reduced to normal. Finally DDAVP became unnecessary. Although the exact cause of DI cannot be ascertained, rapid increase of leukemic blasts and leukostasis in small vessels might be associated with hypothalamus-pituitary system damage. Reportedly, DI is a rare complication of leukemia and administration of DDAVP could be halted in only two patients with leukemia and DI.

L24 ANSWER 3 OF 17 MEDLINE on STN

92177637. PubMed ID: 1795462. [Endogenous vasopressin and fibrinolysis in patients with angina pectoris]. Endogennyi vazopressin i fibrinoliz u bol'nykh so stenokardiei. Averkov O V; Zateishchikov D A; Gratsianskii N A; Dobrovol'skii A B; Panchenko E P; Masenko V P. Kardiologiia, **(1991 Aug)** Vol. 31, No. 8, pp. 11-4. Journal code: 0376351. ISSN: 0022-9040. Pub. country: USSR. Language: Russian.

AB A relationship was examined between **blood vasopressin levels** and the fibrinolytic system in 35 patients with angina pectoris (16 with vasospastic angina (VA) and 19 with exercise-induced angina) who had undergone vein occlusion testing. There was a positive correlation between the post-testing vasopressin levels and the activity of tissue plasminogen activator inhibitor (TPAI) ($r = 0.54$) which was more high in patients with VA ($r = 0.61$). Only did the patients with VA show a direct relationship between the vasopressin concentrations and the activity of tissue plasminogen activator (TPA) ($r = 0.63$), the concentration of fibrinogen-fibrin degradation products (FFDP) ($r = 0.88$). Thirteen patients having higher vasopressin levels (over 3.4 ng/ml) displayed a greater TPAI activity than did the patients with vasopressin levels of at least 3.4 ng/ml (26.2 +/- 4.9 and 15.0 +/- 1.42 IU/ml, respectively; p less than 0.05). There was a direct relationship between the vasopressin levels and the activity of TPA ($r = 0.65$), the concentration of FFDP ($r = 0.78$) in patients having a vasopressin level of above 3.4 ng/ml. The findings are in agreement with the concept that endogenous vasopressin is involved in the regulation of the blood fibrinolytic system.

L24 ANSWER 4 OF 17 MEDLINE on STN

91023165. PubMed ID: 2145777. Role of vasopressin in renal vascular changes with hypoxemia and hypercapnic acidosis in conscious dogs. Rose C E Jr; Ragsdale N V; Carey R M. (Department of Internal Medicine,

University of Virginia School of Medicine, Charlottesville 22908.) The American journal of physiology, **(1990 Oct)** Vol. 259, No. 4 Pt 2, pp. R690-702. Journal code: 0370511. ISSN: 0002-9513.
Report No.: NASA-91023165. Pub. country: United States. Language: English.

AB To evaluate the role of vasopressin in the renal changes during combined acute hypoxemia and acute hypercapnic acidosis, eight conscious female mongrel dogs prepared with controlled sodium intake at 80 meq/24 h for 4 days were studied in one of the following six protocols: acute hypoxemia (80 min, arterial PO2 34 +/- 1 mmHg) followed by combined acute hypoxemia and hypercapnic acidosis (40 min, arterial PO2 35 +/- 1 mmHg, arterial PCO2 58 +/- 1 mmHg, pH = 7.20 +/- 0.01) during 1) intrarenal vehicle at 0.5 ml/min (N = 8); or 2) intrarenal infusion of vasopressin V1-receptor antagonist [d(CH2)5Tyr(Me)]AVP at 5 ng.kg-1.min-1 (N = 5); and with normal gas exchange during 3) intrarenal vasopressin at 0.05 mU.kg-1.min-1 (N = 8); 4) simultaneous infusion of intrarenal vasopressin and [d(CH2)5Tyr(Me)]AVP, 5 ng.kg-1.min-1 (N = 4); 5) intrarenal [d(CH2)5Tyr(Me)]AVP, 5 ng.kg-1.min-1 (N =4); and 6) intrarenal vehicle at 0.5 ml/min (N = 7). Intrarenal infusion of a subpressor dose of vasopressin resulted in a transient decrease in glomerular filtration rate and effective renal plasma flow over the first 20 min of infusion, suggesting that vasopressin induced nonsustained vasoconstriction of the renal vasculature. Intrarenal administration of [d(CH2)5Tyr-(Me)]AVP failed to block the fall in glomerular filtration rate or effective renal plasma flow when renal arterial **blood vasopressin levels** were elevated by intrarenal administration of exogenous vasopressin or by elevated systemic arterial endogenous circulating vasopressin during combined acute hypoxemia and hypercapnic acidosis. These data suggest that vasopressin (V1-receptor stimulation) does not play an important role in the renal vasoconstriction during combined acute hypoxemia and hypercapnic acidosis in conscious dogs.

L24 ANSWER 5 OF 17 MEDLINE on STN
71137380. PubMed ID: 5401935. [Changes in the **blood vasopressin level** following certain balneophysiotherapeutic methods]. Modifications de la teneur en vasopressine sanguine apres certaines methodes balneophysiotherapiques. Modval M; Constantinescu J; Benetato V; Ionescu-Calinesti C. Revue roumaine de physiologie, **(1969)** Vol. 6, No. 4, pp. 285-91.
Journal code: 7510990. ISSN: 0035-399X. Pub. country: Romania. Language: French.

L24 ANSWER 6 OF 17 EMBASE
1990358250 EMBASE Role of vasopressin in renal vascular changes with hypoxemia and hypercapnic acidosis in conscious dogs. Rose Jr. C.E.; Ragsdale N.V.; Carey R.M.. C.E. Rose Jr., Division of Pulmonary Medicine, Box 225, University of Virginia, Health Sciences Center, Charlottesville, VA 22908, United States. American Journal of Physiology - Regulatory Integrative and Comparative Physiology Vol. 259, No. 4 28-4, pp. R690-R702 **1990.**
ISSN: 0002-9513. CODEN: AJPRDO
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 911213. Last Updated on STN: 911213

AB To evaluate the role of vasopressin in the renal changes during combined acute hypoxemia and acute hypercapnic acidosis, eight conscious female mongrel dogs prepared with controlled sodium intake at 80 meq/24 h for 4 days were studied in one of the following six protocols: acute hypoxemia (80 min, arterial PO(2) 34 ± 1 mmHg) followed by combined acute hypoxemia and hypercapnic acidosis (40 min, arterial PO(2) 35 ± 1 mmHg, arterial PCO(2) 58 ± 1 mmHg, pH = 7.20 ± 0.01) during 1) intrarenal vehicle at 0.5 ml/min (N = 8); or 2) intrarenal infusion of vasopressin V(1)-receptor antagonist [d(CH(2))(5)Tyr(Me)]AVP at 5 ng.ovrhdot.kg(-)1.ovrhdot.min(-1) (N = 5); and with normal gas exchange during 3) intrarenal vasopressin at 0.05 mU.ovrhdot.kg(-1).ovrhdot.min(-1) (N = 8); 4) simultaneous infusion of intrarenal vasopressin and

[d(CH(2))(5)Tyr(Me)]AVP, 5 ng.ovrhdot.kg(-1).ovrhdot.min(-1) (N = 4); 5) intrarenal [d(CH(2))(5)Tyr(Me)]AVP, 5 ng.ovrhdot.kg(-1).ovrhdot.min(-1) (N = 4); and 6) intrarenal vehicle at 0.5 ml/min (N = 7). Intrarenal infusion of a subpressor dose of vasopressin resulted in a transient decrease in glomerular filtration rate and effective renal plasma flow over the first 20 min of infusion, suggesting that vasopressin induced nonsustained vasoconstriction of the renal vasculature. Intrarenal administration of [d(CH(2))(5)Tyr(Me)]AVP failed to block the fall in glomerular filtration rate or effective renal plasma flow when renal arterial **blood vasopressin levels** were
elevated by intrarenal administration of exogenous vasopressin or by elevated systemic arterial endogenous circulating vasopressin during combined acute hypoxemia and hypercapnic acidosis. These data suggest that vasopressin (V(1)-receptor stimulation) does not play an important role in the renal vasoconstriction during combined acute hypoxemia and hypercapnic acidosis in conscious dogs.

L24 ANSWER 7 OF 17 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
1978:245336 Document No.: PREV197866057833; BA66:57833. DEVICE FOR THE BIOASSAY OF VASOPRESSIN LEVEL IN BLOOD. HOLOVCHENKO S F [Reprint author]; MASHEK V O; NESTEROVS'KYI M V. LAB PHYSIOL, INST GERONTOL, ACAD MED SCI USSR, KIEV, USSR. Fiziolohichnyi Zhurnal (Kiev), (**1977**) Vol. 23, No. 5, pp. 707-708.
CODEN: FZUKAM. ISSN: 0015-3311. Language: UKRAINIAN.
AB Bioassay of human **blood vasopressin levels**
on rats is based on its diuretic effect. A 5-channel device for registering diuresis continuously for 6-10 h with an accuracy of 0.02 ml is described. The device can also be used for the graphic registration of drops of other electroconductive fluids.

L24 ANSWER 8 OF 17 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
1978:171161 Document No.: PREV197865058161; BA65:58161. STUDIES ON THE ROLE OF HIGH PRESSURE BARO RECEPTORS IN VASOPRESSIN SECRETION EFFECT OF OCCLUSION OF COMMON CAROTID AND VERTEBRAL ARTERIES ON **BLOOD VASOPRESSIN LEVEL.** MATSUZAKI M [Reprint author]. SECOND DEP SURG, NAGOYA UNIV SCH MED, NAGOYA, AICHI, JPN. Folia Endocrinologica Japonica, (**1977**) Vol. 53, No. 8, pp. 982-989.
CODEN: NNGZAZ. ISSN: 0029-0661. Language: JAPANESE.
AB The role of baroreceptors, in common carotid and vertebral arteries and arteries in the thoracic cavity, in vasopressin [ADH] secretion was investigated. Effects of bilateral occlusion of the common carotid and vertebral arteries on blood ADH levels and mean arterial pressure [MAP] were studied in common carotid arterial plexus-denervated dogs, cervically vagotomized dogs and intact dogs. Blood ADH titers were determined by bioassay before and 5 min after the occlusion of the arteries and were compared with the changes of MAP. Blood ADH titers and MAP were elevated by the occlusion of the common carotid arteries in intact and vagotomized dogs, while they were not significantly affected in denervated dogs. Elevation of blood ADH titers was more pronounced in vagotomized dogs than in intact dogs. Blood ADH titers and MAP were elevated by the occlusion of vertebral arteries in all dogs. The elevation of blood ADH titers in denervated dogs was more pronounced than in intact dogs, but less than in vagotomized dogs. The effects of common cartid artery occlusion on blood ADH titers and MAP were more pronounced than those of the vertebral artery occlusion. Baroreceptors involved in vasopressin secretion are present in vertebral arteries and the intrathoracic baroreceptors are dominant in controlling vasopressin secretion, while those in common carotid arteries are of secondary importance and those in vertebral arteries are less important.

L24 ANSWER 9 OF 17 SCISEARCH COPYRIGHT (c) 2008 The Thomson Corporation on STN
1992:677254 The Genuine Article (R) Number: JX717. EFFECT OF PARATHYROID-HORMONE ON CA-45(2+) ACCUMULATION NEUROSECRETORY-CELLS AND ON **BLOOD VASOPRESSIN LEVELS** AFTER

PARATHYROIDECTOMY AND INJECTION OF PARATHYROID EXTRACT. KHUDAVERDYAN D N (Reprint); ASRATYAN A A. YEREVAN PHYS INST, DEPT NORMAL PHYSIOL, YEREVAN, ARMENIA, USSR (Reprint). BULLETIN OF EXPERIMENTAL BIOLOGY AND MEDICINE (**MAR 1992**) Vol. 113, No. 3, pp. 289-291. ISSN: 0007-4888. Publisher: PLENUM PUBL CORP, CONSULTANTS BUREAU 233 SPRING ST, NEW YORK, NY 10013. Language: English.

L24 ANSWER 10 OF 17 SCISEARCH COPYRIGHT (c) 2008 The Thomson Corporation on STN

1986:525566 The Genuine Article (R) Number: D9177. **BLOOD VASOPRESSIN LEVELS** IN RELATION TO OTHER HORMONES IN CORONARY PATIENTS. DUDAEV V A (Reprint); GORIN V V; BORODKIN V V; DYUKOV I V; NECHAEVA N I. NI PIROGOV MED INST, FAC MED, DEPT INTERNAL DIS 1, MOSCOW, USSR (Reprint). KARDIOLOGIYA (**JUL 1986**) Vol. 26, No. 7, pp. 98-101. ISSN: 0022-9040. Publisher: IZD VO MEDITSINA, PETROVERIGSKII PER 6-8, K-142 MOSCOW, RUSSIA. Language: Russian.

L24 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2008 ACS on STN

1997:297524 Document No. 126:272593 Calcium-parathyroid hormone system in the functional activity of the hypothalamic-neurohypophysial complex. Khudaverdyan, D. N.; Asratyan, A. A. (Erevan. Gos. Med. Univ., Yerevan, Armenia). Byulleten Eksperimental'noi Biologii i Meditsiny, 122(11), 484-486 (Russian) **1996.** CODEN: BEBMAE. ISSN: 0365-9615. Publisher: Meditsina.

AB The effect of single and multiple i.m. administration of parathormone on protein synthesis in neurosecretory cells of the supraoptic nucleus and blood vasopressin content was investigated in rats. Parathormone administration increased RNA expression in supraoptic nucleus cells and **blood vasopressin levels**, especially on single administration.

L24 ANSWER 12 OF 17 CAPLUS COPYRIGHT 2008 ACS on STN

1992:34845 Document No. 116:34845 Hormonal indexes of the reactivity of central parts of hypothalamo-hypophyseal-adrenocortical system in rats during postnatal life. Danilova, O. A.; Chernigovskaya, E. V.; Chetverukhin, V. K. (Inst. Evol. Physiol. Biochem., Leningrad, USSR). Zhurnal Evolyutsionnoi Biokhimii i Fiziologii, 27(3), 308-13 (Russian) **1991.** CODEN: ZEBFAJ. ISSN: 0044-4529.

AB ACTH and vasopressin were determined in the blood and pituitary glands of adult male rats as well as in 1-, 3-, 5-, 7-, and 20-day-old rat pups and in the pups at 30 min after surgical stress (cutting skin on the back). The ACTH level in the blood at 1 day of age was 25 pg/mL increasing to a maximum of 279 pg/mL in the adult. Pituitary ACTH levels reached a peak of 17,500 pg/100 g at 20 days of age. Blood vasopressin showed peak levels of 13.0 and 14.2 pg/mL in 5-day-old and adult rats; pituitary levels generally decreased from birth to adult. Surgical stress decreased ACTH secretion in 1-5-day-old rats, increased it in 7-day-old animals, and decreased it in 20-day-old and adult animals. Pituitary levels of ACTH increased in 3-day-old animals and decreased in 7-day-old animals in response to stress. **Blood vasopressin levels** were decreased in 3-day-old rats, but were increased in 7-day-old rats in response to stress. In the pituitary, vasopressin levels were increased in 5- and 20-day-old rats. Vasopressin increased in the median eminence of 1-, 3-, and 20-day old rats in response to stress. Thus, the early period of development of the adrenal cortex-hypothalamus-pituitary system is characterized by a paradoxical reaction rather than by nonreactivity which may be associated with poor neurohormonal transport in the outer zone of the median eminence.

L24 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2008 ACS on STN

1988:469548 Document No. 109:69548 The content of vasopressin in the rabbit's blood plasma after the action of ionizing radiation. Gzirishvili, N. A.; Kebuladze, G. I.; Kabzinadze, K. G. (I. S. Beritashvili Inst. Physiol., Tbilisi, USSR). Izvestiya Akademii Nauk Gruzinskoi SSR, Seriya Biologicheskaya, 14(2), 82-7 (Russian) **1988**

. CODEN: IGSBDO. ISSN: 0321-1665.
AB Whole body exposure of rabbits to x-irradiation (4-8 Gy) or local x-irradiation of the head (8 Gy) altered vasopressin levels in the blood. At 30 min after both whole body and local irradiation, **blood vasopressin levels** were decreased; this was followed, at 2 h, by a marked increase above initial levels. In rabbits with more severe irradiation damage (whole body and local exposure to 8 Gy x-irradiation) **blood vasopressin levels** were elevated between 5 and 30 days after exposure, whereas in animals exposed to whole body-irradiation at 4 Gy they were below normal between 10 and 30 days after exposure. These changes in vasopressin secretion following irradiation may be related to the regulation of metabolic processes in the development of adaptive, compensatory, and reparative processes during radiation disease.

L24 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2008 ACS on STN
1985:572535 Document No. 103:172535 Original Reference No. 103:27583a,27586a Vasopressin effect on the cardiovascular system and electrical activity of the hypothalamus in rabbits of different age. Pugach, B. V. (Inst. Gerontol., Kiev, USSR). Fiziologicheskii Zhurnal (Kiev, 1978-1993), 31(4), 429-33 (Russian) **1985.** CODEN: FIZHDO. ISSN: 0201-8489.
AB Variations in the hemodynamics and elec. activity of the hypothalamus evoked by a single i.v. injection of vasopressin [11000-17-2] (0.2 units/kg) into 10-12- and 48-60-mo-old rabbits were studied. Vasopressin increased arterial pressure and general peripheral resistance, decreased heart min. volume, caused bradycardia, and depressed the S-T segment of the electrocardiograph. The cardiovascular effects were usually more expressed in senescent than in mature animals. Vasopressin also altered (generally decreased) the elec. activity of the supraoptic and ventromedial nuclei of the hypothalamus, effects which were usually more expressed in mature than in senescent animals. The results were related to the increase in **blood vasopressin levels** observed in senescence.

L24 ANSWER 15 OF 17 CAPLUS COPYRIGHT 2008 ACS on STN
1970:19760 Document No. 72:19760 Original Reference No. 72:3589a,3592a Vasopressin content in the hypothalamus, hypophysis, and blood plasma in the guinea pig. Guzek, Jan W. (Sch. Med., Lodz, Pol.). Annals of the Medical Section of the Polish Academy of Sciences, 13(2), 175-205 (English) **1969.** CODEN: ALMPBF. ISSN: 0048-4733.
AB The vasopressin content in the hypothalamus, hypophysis and blood plasma was determined in hydrated and dehydrated guinea pigs under various conditions of adrenergic transmission. In the hydrated guinea pigs, plasma vasopressin level drops below the threshold sensitivity of the assay. After 5 days of dehydration, a marked decrease in the vasopressin content in the hypothalamus accompanied by a distinct rise in the blood level was observed A single dose of reserpine and amphetamine, resp., causes, in hydrated guinea pigs, a marked diminution in the vasopressin content in the hypothalamus and an increase in the **blood vasopressin level.** Reserpine and amphetamine administered to guinea pigs dehydrated for 5 days result, in an increase of the vasopressin release from the hypothalamo-hypophyseal system as compared with animals simply dehydrated. It is supposed that the increased vasopressin release following reserpine administration might be due to the inhibition of adrenergic inhibitory neurons. Similarly, increased vasopressin liberation which follows treatment with amphetamine, might be due to the activation of adrenergic excitatory neurons.

L24 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2008 ACS on STN
1969:409946 Document No. 71:9946 Original Reference No. 71:1819a,1822a Release of vasopressin in response to hemorrhage and its role in the mechanism of blood pressure regulation. Rocha e Silva, Mauricio; Rosenberg, Manuela (Med. Sch., Sao Paulo Univ., Sao Paulo, Brazil). Journal of Physiology (Cambridge, United Kingdom), 202, 535-57 (English) **1969.** CODEN: JPHYA7. ISSN: 0022-3751.

AB The release of vasopressin in response to hemorrhage and the effects of vasopressin infusions on blood pressure and heart rate were studied in dogs. Decrease in diastolic blood pressure of 21-30 mm. elicited increases in blood levels of vasopressin from a control value of 12.8 to 64.8 and 28.5 microunits/ml. in 5- and 30-min. hemorrhage blood samples, resp. Re-transfusion of blood restored vasopressin to control levels. Infusions of vasopressin in amts. secreted in response to hemorrhage evoked vasopressor responses when blood-pressure regulating reflexes were suppressed in reserpinized and atropinized dogs. The role of the secretion of endogenous vasopressin by the pituitary gland in the regulation of blood pressure was also studied in hypophysectomized and deafferented (bilaterally divided vagal and sinus nerves) dogs. Hypotensive responses were paralleled by decreases in **blood vasopressin levels.** Therefore, the release of vasopressin in response to stimuli from cardiovascular sensory receptors is involved in blood-pressure regulation.

L24 ANSWER 17 OF 17 CAPLUS COPYRIGHT 2008 ACS on STN
1965:473730 Document No. 63:73730 Original Reference No. 63:13648f-g The effects of calcium on protein-binding and metabolism of arginine vasopressin in rats. Smith, M. W.; Thorn, N. A. (Univ. Copenhagen). Journal of Endocrinology, 32(2), 141-51 (Unavailable) **1965.** CODEN: JOENAK. ISSN: 0022-0795.
AB cf. CA 63, 8923b. In rats made hypercalcemic by intravenous CaCl2 injection, then given vasopressin intravenously, **blood vasopressin levels** fell more slowly than in normocalcemic controls. In the 30 min. following injection, average urinary excretion by controls was equivalent to 7% of the vasopressin given, and that by hypercalcemic rats was 24%. In controls, injected vasopressin was distributed in a volume equal to blood volume, but in hypercalcemic rats, the distribution volume was about 3 times as large. Antidiuresis from injection of large amts. of vasopressin into hydrated rats was little affected by blood Ca changes. Intravenous CaCl2 given hydrated rats caused temporary diuresis. Expts. with Sephadex G-25 in vitro showed that both ox neurophysin and rat serum protein bind vasopressin, and that Ca interferes.

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L26 14 L25 AND HUMANIZED ANTI-PTHRP

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L27 ANSWER 1 OF 4 MEDLINE on STN DUPLICATE 1
2005628438. PubMed ID: 16309168. Humanized monoclonal antibody against parathyroid hormone-related protein suppresses osteolytic bone metastasis of human breast cancer cells derived from MDA-MB-231. **Saito Hidemi ; Tsunenari Toshiaki; Onuma Etsuro;** Sato Koh; Ogata Etsuro; Yamada-Okabe Hisafumi. (Pharmaceutical Research Department III, Kamakura Research Laboratories, Chugai Pharmaceutical Co., Ltd., Kamakura, Kanagawa 247-8530, Japan.) Anticancer research, (2005 Nov-Dec) Vol. 25, No. 6B, pp. 3817-23. Journal code: 8102988. ISSN: 0250-7005. Pub. country: Greece. Language: English.
AB BACKGROUND: Parathyroid hormone-related protein (PTHrP) has been implicated in bone metastasis. However, the effects on bone metastasis of blocking the PTHrP function have not been tested in the clinic. Here, the effects of a **humanized anti-PTHrP** monoclonal

antibody (mAb) on bone metastasis in a human xenograft model are shown. MATERIALS AND METHODS: Subline MDA-5a, with high bone metastatic activity, was established from the human breast cancer cell line MDA-MB-231. Mice were injected with MDA-5a and an anti-PTHrP monoclonal antibody (mAb) raised against human PTHrP (1-34); bone metastasis was evaluated by X-ray photography. RESULTS: MDA-5a produced elevated levels of PTHrP, Interleukin 8 (IL-8), IL-6 and matrix metalloproteinase 1 (MMP-1) and frequently metastasized to the bone. Administration of the **humanized anti-PTHrP** mAb significantly suppressed osteolytic bone metastasis of MDA-5a and caused osteogenesis at the sites of metastasis. CONCLUSION: The **humanized anti -PTHrP** mAb was effective against bone metastasis by inducing osteogenesis and, therefore, will provide a new treatment option for bone metastasis in breast cancer.

L27 ANSWER 2 OF 4 MEDLINE on STN DUPLICATE 2

2004546213. PubMed ID: 15517871. Generation of a humanized monoclonal antibody against human parathyroid hormone-related protein and its efficacy against humoral hypercalcemia of malignancy. **Onuma Etsuro** ; Sato Koh; **Saito Hidemi**; **Tsunenari Toshiaki**; Ishii Kimie; Esaki Keiko; Yabuta Naohiro; Wakahara Yuji; Yamada-Okabe Hisafumi; Ogata Etsuro. (Chugai Research Laboratories, Chugai Pharmaceutical Co. Ltd., 200 Kajiwara, Kamakura, Kanagawa, Japan.) Anticancer research, (2004 Sep-Oct) Vol. 24, No. 5A, pp. 2665-73. Journal code: 8102988. ISSN: 0250-7005. Pub. country: Greece. Language: English.

AB A humanized monoclonal antibody against parathyroid hormone-related protein (PTHrP) was generated from the mouse monoclonal antibody raised against the peptide corresponding to the N-terminal 34 amino acids of the human PTHrP [(PTHrP(1-34)]. The humanized antibody interacted with the PTHrP(1-34) with a kD value of 1.90 x 10(-10) M, and the epitope resides between the amino acids 20 and 30 of the PTHrP. PTHrP(1-34) significantly increased the intracellular cAMP levels in the rat osteosarcoma cells that expressed PTHR1, and the 5 microg/mL or higher concentrations of the humanized antibody almost completely blocked the PTHrP-induced cAMP production even in the presence of 2 microg/mL PTHrP(1-34), demonstrating its ability to fully neutralize PTHrP function. There was no significant difference in the potency of the mouse, chimera, or the humanized antibodies to suppress the PTHrP-induced increase in the intracellular cAMP in ROS cells. Furthermore, at the same doses, the administration of the chimera or the humanized antibody was equally effective in reducing the blood ionized calcium levels of hypercalcemic mice bearing the PAN-7-JCK human pancreatic cancer xenograft or the LC-6-JCK human lung cancer xenograft that secreted PTHrP. Thus, **humanized anti-PTHrP** may be useful for the treatment of the humoral hypercalcemia of malignancy in humans.

L27 ANSWER 3 OF 4 MEDLINE on STN DUPLICATE 3

2003534792. PubMed ID: 14613038. Treatment of malignancy-associated hypercalcemia and cachexia with humanized anti-parathyroid hormone-related protein antibody. Sato Koh; **Onuma Etsuro**; Yocum Richard C; Ogata Etsuro. (Department of International Coordination, Chugai Pharmaceutical Co, Ltd, Skizuuoka, Japan.) Seminars in oncology, (2003 Oct) Vol. 30, No. 5 Suppl 16, pp. 167-73. Ref: 11. Journal code: 0420432. ISSN: 0093-7754. Pub. country: United States. Language: English.

AB Parathyroid hormone-related protein (PTHrP) plays a central role in humoral hypercalcemia of malignancy (HHM), which is one of the most frequent paraneoplastic syndromes. PTHrP produced by the tumor acts through a common PTH/PTHrP receptor to promote bone resorption, inhibit calcium excretion from the kidney, and induce hypercalcemia. Patients with HHM often develop cachexia associated with typical symptoms such as anorexia, malaise, nausea, constipation, polyuria, polydipsia, and confusion. The etiology of the cachexia is not fully understood but is thought to be caused by hypercalcemia and various cytokines such as interleukin-6, tumor necrosis factor-alpha, leukemia inhibitory factor, and others. In this study, we investigated the role of PTHrP in

hypercalcemia and cachexia in HHM by using **humanized anti-PTHrP** antibody. A mouse monoclonal antibody that binds to PTHrP amino acid sequence 1-34 and inhibits PTHrP function has been humanized to create a specific and potent agent for the treatment of patients with HHM. The mouse monoclonal antibody has been shown to have antihypercalcemic activity against nude mice bearing human tumors. Because a mouse antibody is highly immunogenic in human patients, the complementarity-determining regions from the mouse antibody were grafted into a human antibody. The resulting humanized antibody specifically recognizes PTHrP(1-34) and neutralizes PTHrP functions in vitro and in vivo. The **humanized anti-PTHrP** antibody was administered intravenously to HHM model animals bearing tumors such as LC-6 human lung carcinoma. These animals showed symptoms similar to those of patients with HHM (eg, hypercalcemia and cachexia). The **humanized anti-PTHrP** antibody-treated animals responded with normalization of blood ionized calcium level through an improvement of bone metabolism and calcium excretion. Moreover, the treated animals also showed an improvement in body weight, ultromotivity, metabolic alkalosis, food consumption, water intake, serum phosphorus, and renal function. Consequently, the humanized antibody-treated animals experienced complete resolution of hypercalcemia and cachexia. These results suggest that the humanized antibody would be an effective and beneficial agent for patients with HHM, and that PTHrP is a major pathogenetic factor of hypercalcemia and cachexia in patients with HHM.

L27 ANSWER 4 OF 4 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
2000:244979 Document No.: PREV200000244979. The possibility of utilizing **humanized anti-PTHrP** antibody as an anti-HHM/cachexia agent. **Onuma, Etsuro** [Reprint author]; **Saito, H.**; **Azuma, Y.**; Shimizu, N.; **Tsunenari, T.**; Sato, K.; Ogata, E.. Chugai Pharmaceutical, Shizuoka, Japan. Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 287. print.
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 01-05, 2000.
ISSN: 0197-016X. Language: English.

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L31 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2008 ACS on STN
2002:888597 Document No. 138:3671 Angiogenesis inhibitors that block binding of PTH-related peptide to its receptor for use as antitumor agents. **Saito, Hidemi**; **Tsunenari, Toshiaki**; **Onuma, Etsuro**; Kato, Atsuhiko; Suzuki, Masami (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2002092133 A1 20021121, 110 pp.
DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC,

ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (Japanese). CODEN: PIXXD2.
APPLICATION: WO 2002-JP4586 20020510. PRIORITY: JP 2001-140659 20010510.

AB It is found out that angiogenesis can be inhibited by a substance which inhibits the binding of a parathyroid hormone-associated peptide (e.g. PTHrP) to its receptor. The angiogenesis inhibitors can be anti-PTHrP antibodies, antibody fragments, humanized or chimeric antibodies, PTH receptor antagonists, or antisense oligonucleotides specific to PTHrP. These modified anti-PTHrP antibodies and PTH receptor antagonists are useful as antitumor agents and bone metastasis inhibitors.

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